Interview Summary Record

On August 31, 2009 the undersigned returned a call from Examiner Anderson. Examiner Anderson indicated that a patentability conference with himself, his supervisor and a third examiner had concluded that there was patentable subject matter in the case but that claims would need to be further restricted. The Examiner suggested to restrict the claims to a treatment of BCC tumor with an exemplified medicament preparation, concentration and treatment regime. Agreement was not reached pending discussions with the Applicant.

Remarks

The Applicant would like to refer to the amendments filed on 29 July 2009 and 18 March 2009 pointing out to the objective facts showing patentability of the claimed subject matter. However, considering comments of the Examiner in the 31 August 2009 interview, further restricted claims 68-71 are filed herewith, reciting the dose forms and dose to be used to achieve decrease of size or disappearance of a tumor described in the exemplifications of invention. Filing of the new claims 68-71 is not to be construed to imply lack of patentability of the previously presented claims. Claim 68 depends from claim 60 and recites a method of treatment of a human bearing a skin tumor, reciting the dose forms to be used. Claim 69, also depending from claim 60, names particular types of skin tumors. Claim 70 depends from claim 69 and further recites a dose amount described in the exemplifications of invention. Claim 71, depending from claim 70, specifies a dose form of cyclopamine described in the exemplifications of invention.

A drug treatment must have acceptable safety and efficacy for use on human. Ratio between a dose that exerts unacceptable toxic effects or lethality and a dose effective to produce a desired therapeutic result is a determinant of the applicability of a drug treatment in general. Dose-dependent adverse effects of conventional cancer chemotherapies on normal stem cells and progenitor cells have long been recognized as a problem limiting their efficacy and utility. Their narrow therapeutic index and dose-limiting adverse effects are problems that are particularly pronounced in human (Takimoto CH, *Clinical Cancer Research* 2001;7:229-230). Yet, normal stem cells were described in prior art to have an absolute dependence on Hedgehog/Smoothened (Hh/Smo) signaling (Zhang Y et al, *Nature* 2001;410:599-604). Thus, in prior art a possible motivation to administer a Hh/Smo signaling inhibitor to a tumor patient in view of the findings of a direct stimulation of cellular proliferation by Hh/Smo signaling would be tempered by expectations of dose-dependent adverse effects and, in any case, a skilled person would not administer beyond a dose inhibiting tumor cell proliferation.

Contrary to the teachings in prior art, on the other hand, present application shows that a selective inhibitor of Hh/Smo signaling can be used to eliminate tumor cells from human patients with unprecedented safety. Even the normal stem cells and multipotent progenitor cells that are particularly damaged by conventional chemotherapy-radiotherapy are shown to be perfectly spared following exposure to an identical or greater dose of cyclopamine causing apoptotic elimination of tumor cells. Induction of apoptosis of tumor cells *in vivo* is shown to require treatment with a dose of medicament far greater than a dose sufficing to consistently inhibit proliferation of the same tumor cells (see the amendments filed on July 29, 2009; March 18, 2009; January 10, 2007). It is shown that normal stem cells and progenitor cells markedly differ from tumor cells in their susceptibility to treatment with a selective inhibitor of Hh/Smo signaling and that a dose beyond that inhibiting tumor cell proliferation can be administered safely and must be administered for eliminating tumor cells from patients. An unprecedented margin of safety with the present method of treatment is also shown. For example, page 11, lines 15-20 describe tumors treated with topical applications of about 10 μl of 18 mM cyclopamine cream four times daily to the skin on tumor. Another similarly sized tumor is described on page 16, lines 25-28 to have received about 25 μl of the same cream eight times in a day. A skilled person sees that whereas the normal skin tissue on and around the latter tumor received about 5 folds greater amount of cyclopamine in a day (25/10 X 8/4 = 5), the normal skin is showing no adverse effects (see page 2/2a, Fig 6B; see also the skin receiving 20 to 25 μl of 18 mM cyclopamine cream six to eight times per day in Fig 5B and Fig 7B and see the description on page 19, lines 21-27). Thus, a wide margin of safety and an advantageous therapeutic index never seen in prior art is described. As explained in Tas S, *Melanoma Research* 2006;16:S99 and in the manuscript of Applicant filed with the June 11, 2007 dated Amendment, an essential difference of the tumorigenic cells having stem cell features from normal stem cells makes the tumorigenic cells fundamentally vulnerable and selectively eliminated upon treatment by the present method.

New claims 68 and 69 recite treatment of a human subject having a skin tumor as described in the specification of application and shown in the exemplifications of invention. The particular dose recitation in claim 70 is from the exemplifications of invention. In an example given on page 11, lines 15-20, it is described that the tumor was treated by topical applications of about 10 μl of 18 mM cyclopamine cream to 4 X 5 mm skin surface area four times daily. Said applications can be calculated to deliver about 3.6 micromole of cyclopamine per day to each square centimeter of the surface area of tumor on skin (10 X 4 = 40 μl cream to 20 mm2 = 0.2 cm2 per day which is 40 X 1/0.2 = 200 μl cream to a cm2 per day; 0.2 ml of 18 mM cream has 3.6 micromole of cyclopamine). The pharmaceutical form recited in new claim 71 has the same exemplification support.

A person skilled in the art routinely administers a prior art medicament to a patient to cause a previously known and expected effect or therapeutic result. Once informed about the effects and therapeutic results to be caused, a skilled person can readily optimize the dose of a medicament for a patient taking into account his/her body mass, age and other particulars regularly considered in dose optimization. The present application teaches directly and unambiguously the technical effects and therapeutic results that can be caused by the claimed method of treatment and shows exemplifications with several tumor patients. Thus, a person of ordinary skill in the art reading the originally filed application can readily carry out the invention. A skilled person understands from the specification that the particular dose form and amount recited in claim 70 is exemplary (rather than restrictive) and that the natural variation of patients in their physical features and physiological functions calls for optimization of dose in a patient (see e.g. page 11, lines 10-15). From a therapeutic viewpoint, the described wide margin of safety simplifies the use of present method and, as pointed out in the specification, a perfect preservation of normal cells under the described conditions shown to eliminate tumor cells facilitates and guides other modes of administration (page 11, lines 22-27; page 15, lines 19-24; page 19, line 27 to page 20, line 8). From a patentability viewpoint, it is clear that neither the claimed technical effects and therapeutic results nor the means to achieve them were known or described in prior art. It is further clear that the presently claimed technical effects and therapeutic results are not inherently present in a prior art use described for a selective inhibitor of Hh/Smo signaling and that the minimal dose effective for inducing apoptosis of tumor cells is magnitudes greater than the minimal dose effective for inhibiting proliferation of the same cells.

At least for the reasons given above and articulated with the amendments filed on March 18, 2009 and July 29, 2009, the new claims 68-71 as well as the previously presented claims 44-67, describe patentable subject matter.

Respectfully submitted,
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